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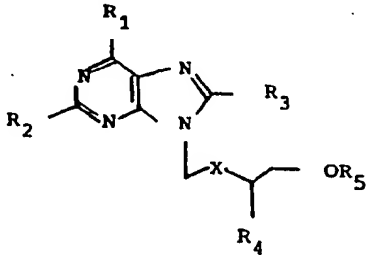
(54) **Purine derivatives and an intermediate in the production thereof.**

(57) Novel purine derivatives of formula



as agents for treating autoimmune diseases are described. Also disclosed are processes for their production and pharmaceutical compositions comprising the compounds, as well as novel intermediates in the manufacture thereof.

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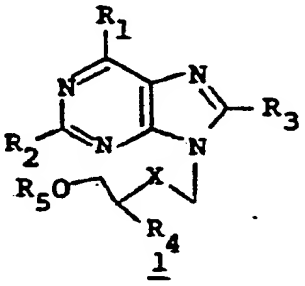
PURINE DERIVATIVES AND AN INTERMEDIATE IN THE PRODUCTION THEREOF

The present invention relates to a compound of the formula



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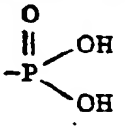
wherein R_1 is OH or SH; R_2 is hydrogen, NHR in which R is hydrogen or COR_6 where R_6 is alkyl of 1-4 carbon atoms, aryl or arylalkyl; R_3 is bromine or NHR where R is hydrogen or COR_6; X is O or S; R_4 is hydrogen or CH_2OR_5 in which R_5 is hydrogen, alkyl of 1-8 carbon atoms, aryl



arylalkyl, or COR_6, or a pharmaceutically

acceptable acid or base addition salt thereof.

In a second generic aspect, the present invention relates to a compound of the formula I, wherein R_1 is OH or SH; R_2 is hydrogen or NHR in which R is hydrogen or COR_6 where R_6 is alkyl of one to four carbon atoms, aryl or arylalkyl; R_3 is hydrogen; X is O or S; R_4 is alkyl of one to eight carbon atoms, aryl or arylalkyl, and R_5 is hydrogen, or a pharmaceutically acceptable acid or base addition salt thereof.

In a third generic aspect, the present invention relates to a compound of the formula I, wherein R_1 is OH or SH; R_2 is hydrogen or NHR in which R is

hydrogen or COR_6 where R_6 is alkyl of one to four carbon atoms, aryl or arylalkyl; R_3 is hydrogen; X is O or S; R_4 is CH_2OR_7 in which R_7 is alkyl of one to eight carbon atoms, cycloalkyl of five to seven ring members, cycloalkylalkyl, aryl or arylalkyl, and R_5 is hydrogen, or a pharmaceutically acceptable acid or base addition salt thereof.

The present invention includes a method of manufacture, pharmaceutical composition comprising an effective amount of a compound of the formula 1 in all three generic aspects with a pharmaceutically acceptable carrier, as well as a method of treatment of autoimmune diseases such as arthritis, systemic lupus erythematosus, inflammatory bowel diseases, transplantation, juvenile diabetes, myasthenia gravis, multiple sclerosis as well as viral infections and cancer by administering an effective amount of a compound of the formula 1 in all three generic aspects in unit dosage form.

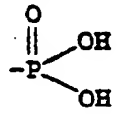
The term "alkyl of 1-8 carbon atoms" means a straight or branched hydrocarbon chain up to 8 carbon atoms such as, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tertiary-butyl, or octyl.

The term "cycloalkyl of five to seven ring members" means cyclopentyl, cyclohexyl, or cycloheptyl.

The term "cycloalkylalkyl" means a cyclopentyl, cyclohexyl, or cycloheptyl radical attached to an alkyl chain of up to four carbon atoms, straight or branched, such as for example, cyclohexylmethyl or cyclohexylethyl.

The term "aryl" includes unsubstituted and substituted aromatic ring such as, phenyl or phenyl substituted by halo, e.g., fluoro, chloro, bromo, or alkyl of 1-4 carbon atoms, such as methyl or ethyl, hydroxy, alkoxy of 1-4 carbon atoms, such as methoxy or ethoxy, or trifluoromethyl.

The term "arylalkyl" means an aromatic ring attached to an alkyl chain of up to 4 carbon atoms, such as unsubstituted or substituted phenylethyl or benzyl where the substituents on the aromatic ring may be the same as defined above.

Pharmaceutically acceptable base salts of the phosphate ester, where R_5 is  are the alkali metals, ammonium or substituted ammonium salts, such as sodium, potassium, and ammonium salts. The base salts may be prepared by standard methods known in the art.

Pharmaceutically acceptable acid addition salts are those derived from inorganic acids such as hydrochloric, sulfuric and the like, as well as organic acids such as methanesulfonic, toluenesulfonic, tartaric acid, and the like. These salts may also be prepared by standard methods known in the art.

Other pharmaceutically acceptable salts are those derived from inorganic bases such as sodium hydroxide, potassium hydroxide or ammonium hydroxide or organic bases such as arginine, N-methyl glucamine, and the like. These salts may also be prepared by standard methods known in the art.

A preferred embodiment of the present invention in its first generic aspect is a compound of formula 1 wherein R_1 is OH or SH; R_2 is hydrogen or NHR in which R is hydrogen or COR_6 where R_6 is alkyl of 1-4 carbon atoms or phenyl; R_3 is bromine or NH_2; X is O

or S; R_4 is hydrogen or CH_2OR_5 in which R_5 is hydrogen, alkyl of 1-8 carbon atoms, benzyl or phenyl, or a pharmaceutically acceptable acid addition or base salt.

Another preferred embodiment of the present invention in its first generic aspect is a compound of formula 1 wherein R_1 is OH; R_2 is hydrogen or NH_2; R_3 is bromine or NH_2; X is O; R_4 is hydrogen or CH_2OR_5 in which R_5 is hydrogen or a pharmaceutically acceptable acid addition or base salt.

Particular embodiments of the present invention in its first generic aspect include 2,8-diamino-9-[(2-hydroxyethoxy) methyl]-9H-purin-6-ol, 2-[(2,8-diamino-6-hydroxy-9H-purin-9-yl)methoxy]-1,3-propanediol, 2,8-diamino-1,9-dihydro-9-[[1-(hydroxymethyl)-2-phenoxyethoxy)methyl]-6H-purin-6-one and 2-[(2-amino-8-bromo-6-hydroxy-9H-purin-9-yl)methoxy]-1,3-propanediol. The latter compound is not only useful pharmacologically but is also useful as an intermediate for preparing certain compounds of the present invention.

A preferred embodiment of the present invention in its second generic aspect is a compound of formula 1, wherein R_1 is OH; R_2 is hydrogen or NHR in which R is hydrogen or COR_6 where R_6 is alkyl of one to four carbon atoms, phenyl or benzyl; R_3 is hydrogen; X is O; R_4 is alkyl of one to eight carbon atoms, phenyl or benzyl, and R_5 is hydrogen, or a pharmaceutically acceptable acid addition or base salt.

Another preferred embodiment of the present invention in its second generic aspect is a compound of formula 1, wherein R_1 is OH; R_2 is hydrogen or NHR in which R is hydrogen or COR_6 where R_6 is methyl; R_3 is hydrogen; X is O; R_4 is alkyl of four to eight carbon atoms, phenyl or benzyl, and R_5 is

hydrogen or a pharmaceutically acceptable acid addition or base salt.

Particular embodiments of the present invention in its second generic aspect include 2-amino-1,9-dihydro-9-[[[1-(hydroxymethyl)hexyl]oxy]methyl]-6H-purin-6-one and 2-amino-1,9-dihydro-9[[[1-(hydroxymethyl)nonyl]oxy]methyl-6H-purin-6-one. The above compounds are not only useful pharmacologically but are also useful as intermediates for preparing certain compounds of formula 1 of the present invention in its first generic aspect.

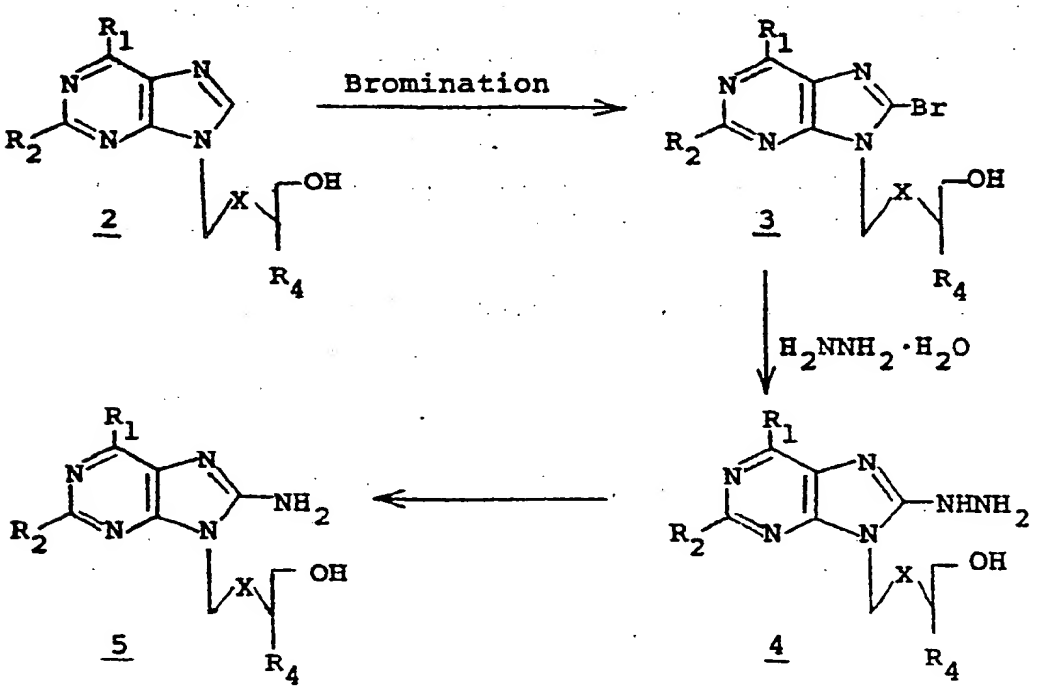
A preferred embodiment of the present invention in its third generic aspect is a compound of formula 1, wherein R_1 is OH; R_2 is hydrogen or NHR in which R is hydrogen or COR_6 where R_6 is alkyl of one to four carbon atoms, phenyl or benzyl; R_3 is hydrogen; X is O; R_4 is CH_2OR_7 in which R_7 is alkyl of one to eight carbon atoms, cycloalkyl of five to seven ring members, cycloalkylalkyl, phenyl or benzyl, and R_5 is hydrogen, or a pharmaceutically acceptable acid addition or base salt.

Another preferred embodiment of the present invention in its third generic aspect is a compound of formula 1, wherein R_1 is OH; R_2 is hydrogen or NHR in which R is hydrogen or COR_6 where R_6 is methyl; R_3 is hydrogen; X is O; R_4 is CH_2OR_7 in which R_7 is alkyl of two to eight carbon atoms, cyclopentyl, cyclohexyl, cyclopentylmethyl, cyclohexylmethyl, phenyl or benzyl, and R_5 is hydrogen, or a pharmaceutically acceptable acid addition or base salt.

Particular embodiments of the present invention in its third generic aspect include 2-amino-9[[2-(cyclohexylmethoxy)-1-(hydroxymethyl)ethoxy]methyl]-1,9-dihydro-6H-purin-6-one;
2-amino-9-[[2-(hexyloxy)-1-(hydroxymethyl)ethoxy]methy]-1,9-dihydro-6H-purin-6-one;

2-amino-9-[[2-heptyloxy)-1-(hydroxymethyl)ethoxy] methyl]-1,9-dihydro-6H-purin-6-one;
2-amino-1,9-dihydro-9-[[1-(hydroxymethyl)-2-(pentyl-oxy)ethoxy]methyl]-6H-purin-6-one;
2-amino-1,9-dihydro-9-[[1-(hydroxymethyl)-2-(octyloxy) ethoxy]methyl]-6H-purin-6-one, and
2-amino-1,9-dihydro-9-[[1-hydroxymethyl)-2-(phenoxy) ethoxy]methyl]-6H-purin-6-one.

The compounds of formula 1 may be prepared according to the following scheme:

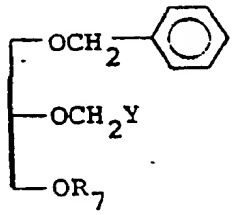


The compounds of formula 2 above where R_1 = OH, R_2 = NH_2, X = O, R_4 = H or CH_2OH may be prepared according to British Patent Specification 1,567,671 or J. C. Martin, et al, in J Med Chem 26, 759 (1983). The remainder of the compounds of formula 2 above used as starting materials and final products are prepared according to the schemes 1 and 2. Treatment of a compound of formula 2 with N-bromosuccinimide in

acetic acid, DMF or m thanol produces a compound of formula 3 which when treated with hydrazine hydrate gives the hydrazine of formula 4 or directly the 8-amino derivative of formula 5. The reaction of the 8-bromo compound with hydrazine may or may not proceed entirely to the 8-amino compound. Thus when the 8-hydrazine compound is obtained, it may be further reacted with Raney nickel to allow the reduction to go to completion and afford the desired 8-amino compound. Compounds of formula 5 wherein R_1, R_2, and R_4 have been defined according to compounds of formula 1 may be further converted by known methods to provide R_5 substituents of formula 1 or, for example, where R_1 is OH, converting said compound to a compound of formula 1 where R_1 is SH by known means.

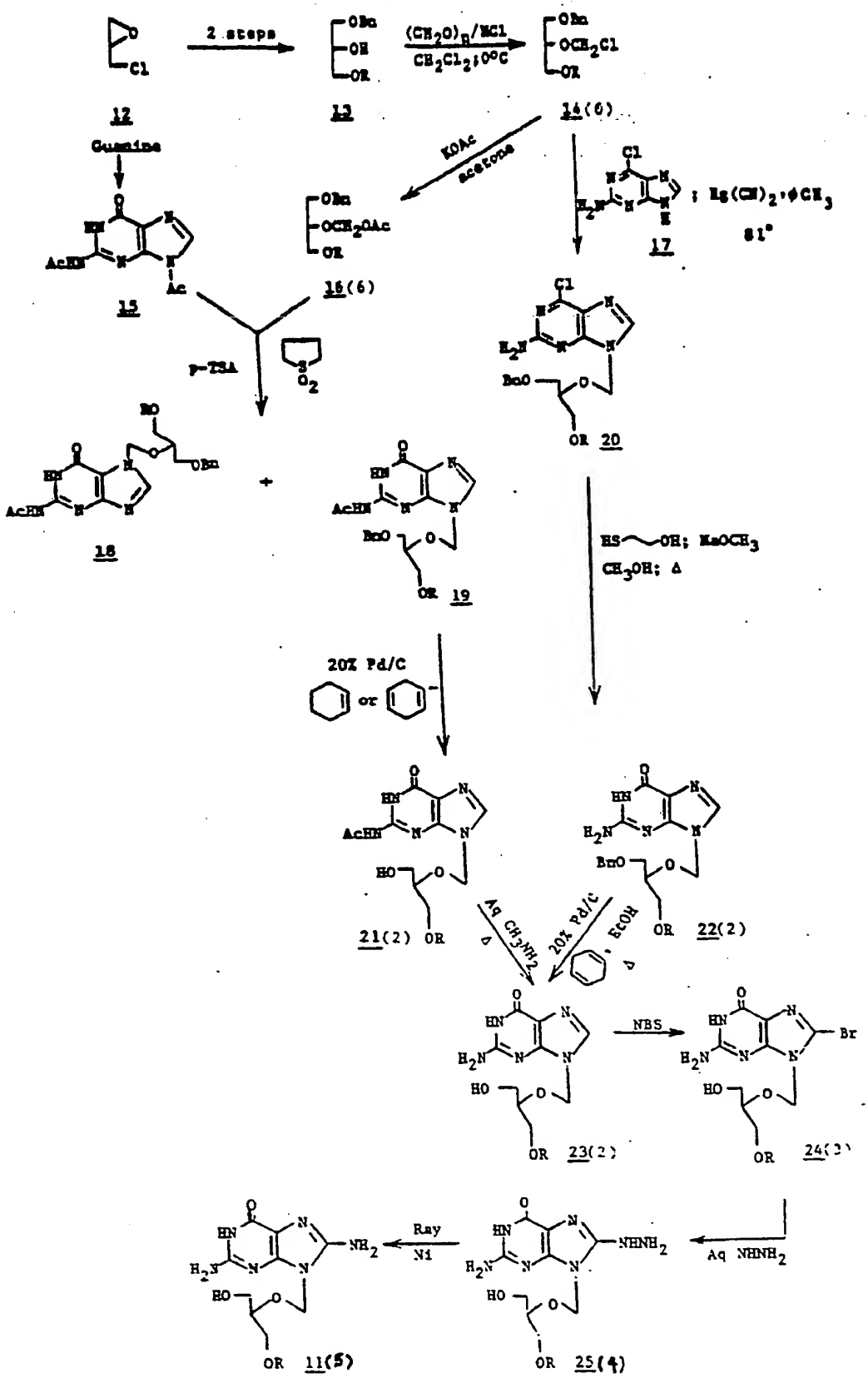
The compounds of the present invention and of the formulae 1, 2, 3, 4, and 5, shown above, may also be prepared by the following schematic sequences of reaction steps as illustrated in Schemes 1 and 2. The numbers in parentheses toward the end of each reaction scheme correspond to the compounds of the present invention as defined above. A more detailed description of the reaction steps is provided in the Examples.

In the preparation of compounds of the present invention and of the formulae 1 and 5, there are employed novel intermediates which are part of the present invention. These are compounds of the formula

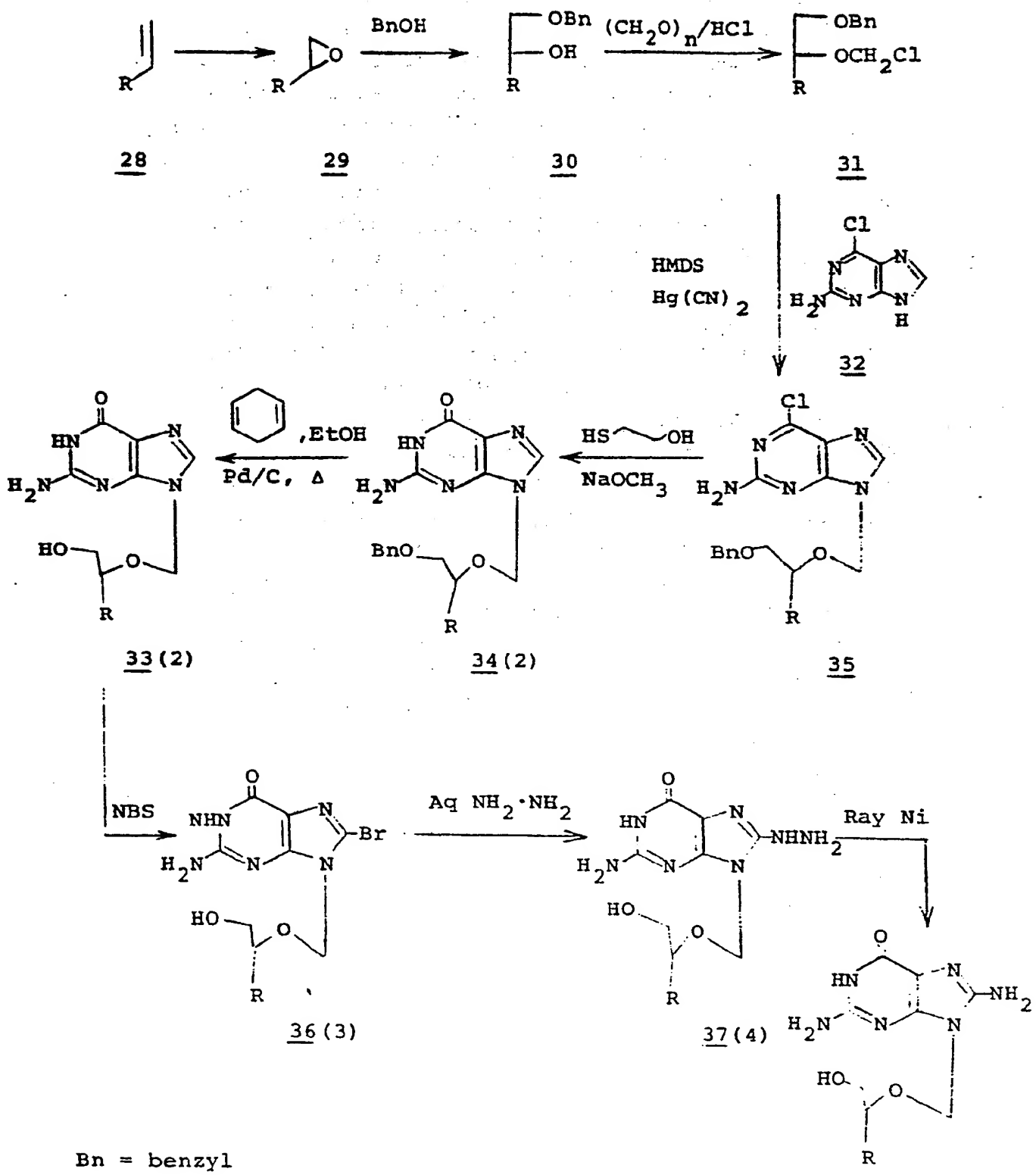


wherein Y is acetyloxy or chloro and R_7 is alkyl of one to eight carbon atoms, cycloalkyl of five to seven ring members, cycloalkylalkyl, aryl or arylalkyl. Preferably, R_7 is alkyl of two to eight carbon atoms, cyclopentyl, cyclohexyl, cyclopentylmethyl, cyclohexylmethyl, phenyl or benzyl.

Scheme 1


2 steps
$(CH_2O)_n$/HCl
CH_2Cl_2;0°C
12
13
14(6)
Guanine
KOAc
acetone
15
16(6)
17
$Mg(CH_2)_2$,ϕCH_3
81°
p-TSA
18
19
20
HS~OH; $NaOCH_3$
CH_3OH; Δ
20% Pd/C
or
21(2)
22(2)
Aq CH_3NH_2
Δ
20% Pd/C
EtOH
Δ
NBS
23(2)
24(2)
Aq $NHNH_2$
Ray Ni
11(5)
25(4)

Scheme 2



Bn = benzyl

The compounds of the present invention have been shown to exhibit significant enzyme inhibition activity and cytotoxic activity. In the purine nucleoside phosphorylase (PNP-4) enzyme assay, total inhibition was achieved at a concentration less than about 300 micromoles on certain compounds. The same compounds also were found by a standard test (Science, 214, 1137, 1981) to be selectively cytotoxic for T-cells in the presence of 2'-deoxyguanosine at a similar concentration range. For example, 2,8-diamino-9-[(2-hydroxyethoxy)methyl)]-9H-purine-6-ol is selectively cytotoxic to T-cell at a concentration of about 30 micromoles in the presence of 10 micromoles of 2'-deoxyguanosine. Similarly, 2-[(2,8-diamino-6-hydroxy-9H-purin-9-yl)methoxy]-1,3-propanediol is selectively cytotoxic to T-cell at a concentration of about 7 micromoles in the presence of 10 micromoles of 2'-deoxyguanosine. Both compounds were nontoxic to B-cell in the presence of the same amount of 2'-deoxyguanosine. Since T-cells play a central role in immune response, use of the compounds of the invention is contemplated for the immunoregulation of autoimmune disease such as rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, cancer, and viral diseases, transplantation, juvenile diabetes, myasthenia gravis, and multiple sclerosis. The present invention thus includes compositions containing a compound of formula 1 in treating disease such as autoimmune disease characterized by abnormal immune response in warmblooded animals. According to this aspect of the invention, the properties of the compounds of the invention are utilized by administering to a warm-blooded animal an effective

amount of a pharmaceutical composition containing as the active ingredient at least about 0.1 percent by weight, based on the total weight of the composition of at least one such compound of the invention.

Pharmaceutical compositions of the invention can be formulated in any suitable way, preferably with an inert carrier for administration orally, parenterally, ophthalmically, topically, or by suppository.

For example, the compounds of the present invention are formulated into dosage forms such as tablets or syrups by blending with an inert pharmaceutical carrier such as lactose or simple syrup by methods well known in the art. For injectionable dosage forms, they are formulated with vehicles such as water, peanut oil, sesame oil, and the like. In these dosage forms, the active ingredient is from about 0.05 grams to 0.5 grams per dosage unit.

The present invention is further illustrated by way of the following examples.

EXAMPLE 1

2-Amino-8-bromo-9-[(2-hydroxyethoxy)methyl]-9H-purin-6-ol[a]

N-bromosuccinimide (0.415 g; 2.3 mmol) is added to a solution of acycloguanosine (0.5 g; 2.2 mmole) (prepared according to British Patent 1,567,671) in acetic acid (7 ml) and the mixture stirred at room temperature for 20 hours. The solution is then diluted with water (20 ml) and the precipitated product is filtered, washed, and triturated with hot water to give 0.25 g of white solid, mp > 300°C.

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[a]...The structure of this compound is disclosed in Biochem. Pharm., 30, 3071-3077 (1981) by P. M. Keller, et. al..

EXAMPLE 1A

The procedure described in Example 1 is repeated to prepare the following 8-bromo-9-substituted guanines starting from appropriate 9-substituted guanines in each case using acetic acid, methanol or DMF as solvent:

2-amino-8-bromo-9-[[2-(heptyloxy)-1-(hydroxymethyl) ethoxy]methyl]-1,9-dihydro-6H-purin-6-one, mp >250°C, dec;

2-amino-8-bromo-9-[[2-(hexyloxy)-1-(hydroxymethyl) ethoxy]methyl]-1,9-dihydro-6H-purin-6-one, mp >250°C, dec;

2-amino-8-bromo-9-[[2-butoxy-1-(hydroxymethyl) ethoxy]methyl]-9H-purin-6-ol, mp >200°C;

2-amino-8-bromo-1,9-dihydro-9-[[1-(hydroxymethyl)-2-(octyloxy)ethoxy]methyl]-6H-purin-6-one, mp 223-226°C, dec;

2-amino-8-bromo-9-[[2-(hexyloxy)-1-(hydroxymethyl) ethoxy]methyl]-1,9-dihydro-6H-purin-6-one, mp 212-214°C;

2-amino-8-bromo-9[[2-ethoxy-1-(hydroxymethyl)ethoxy] methyl]-1,9-dihydro-6H-purin-6-one, mp 217-219°C, dec;

2-amino-8-bromo-1,9-dihydro-9-[[1-(hydroxymethyl)-2-(pentyloxy)ethoxy]methyl]-6H-purin-6-one, mp >250°C, dec;

2-amino-8-bromo-9-[[2-(cyclohexylmethoxy)-1-(hydroxy-methyl)ethoxy]methyl]-1,9-dihydro-6H-purin-6-one, mp 210-212°C (dec);

2-amino-8-bromo-1,9-dihydro-9-[[1-(hydroxymethyl)-2-(phenoxy)ethoxy]methyl]-6H-purin-6-one, mp 218-219°C, dec;

2-amino-8-bromo-1,9-dihydro-9-[[2-hydroxy)-1-[(4-methoxyphenoxy)methyl]ethoxy]methyl]-6H-purin-6-one; mp 205-210°C, dec;

2-amino-8-bromo-1,9-dihydro-9-[[1-(hydroxymethyl)-2-(4-methylphenoxy)ethoxy]methyl]-6H-purin-6-one, mp 207-208°C, dec;

2-amino-8-bromo-1,9-dihydro-9-[[2-(4-chlorophenoxy)-1-(hydroxymethyl)ethoxy]methyl]-6H-purin-6-one, and 2-amino-8-bromo-1,9-dihydro-9-[[[1-(hydroxymethyl) nonyl]oxy]methyl]-6H-purin-6-one, mp 211-212°C, dec.

EXAMPLE 2

2,8-Diamino-9-[(2-hydroxyethoxy)methyl)]-9H-purin-6-ol

The crude 2-amino-8-bromo-9-[(2-hydroxy-ethoxy)methyl]-9H-purin-6-ol from acycloguanosine (3.17 g; 0.14 mol) is suspended in water (10 ml) and 97% hydrazine (4 ml) is added to the mixture. The mixture is refluxed for 48 hours, cooled and filtered to give a white solid (1.6 g) which is triturated with hot water (75 ml) to give the analytical sample (1.5 g), mp > 300° dec.

EXAMPLE 3

2-[(2-Amino-8-bromo-6-hydroxy-9H-purin-9-yl)methoxy]-1,3-propanediol

N-bromosuccinimide (0.375 g; 2.1 mmol) is added to a solution of 9'-[(1,3-dihydroxy-2-propoxy) methyl]guanine (0.5 g; 1.9 mmole) [prepared according to J. C. Martin; C. A. Dvorak, D. P. Smee, T. R. Matthews, and J. P. H. Verheyden, J Med Chem 26, 759-761 (1983)] in acetic acid (7 ml). The suspension is stirred for 1.5 hours at room temperature and then diluted with water (60 ml). The aqueous solution is concentrated and the residue is recrystallized from water to give 0.44 g of the product; mp > 300° dec.

EXAMPLE 4

2-[(2,8-Diamino-6-hydroxy-9H-purin-9-yl)methoxy]-1,3-propanediol

A mixture of 2-[(2-amino-8-bromo-6-hydroxy-9H-purin-9-yl)methoxy]-1,3-propanediol (13.7 g; 41 mmole) and 97% hydrazine (6.07 ml) in water (300 ml) is heated to reflux for 48 hours. At the end of this time, the solution is cooled and filtered to give 9.15 g of crude solid. The crude product is suspended in water (120 ml) and Raney nickel (9 g) is added. The mixture is heated at reflux for 6 hours, filtered hot and cooled. The crystals are collected and dried to give 7.15 g of the product, mp > 280° dec.

EXAMPLE 4A

The procedure described in Example 4 is repeated to prepare the following 8-amino-9-substituted guanines starting from appropriate 8-bromo-9-substituted guanines in each case using methoxyethanol as a cosolvent as necessary to make a homogeneous reaction mixture:

2,8-diamino-9-[[2-ethoxy-1-(hydroxymethyl)ethoxy]methyl]-9H-purin-6-ol, mp >220°C, dec;

2,8-diamino-9-[[2-(hexyloxy)-1-(hydroxymethyl)ethoxy]methyl]-1,9-dihydro-6H-purin-6-one, mp >265°C, dec;

2,8-diamino-9-[[2-butoxy-1-(hydroxymethyl)ethoxy]methyl]-9H-purin-6-ol, mp >240°C, dec;

2,8-diamino-1,9-dihydro-9-[[1-(hydroxymethyl)-2-(pentyloxy)ethoxy]methyl]-6H-purin-6-one, mp 274-277°C, dec;

2,8-diamino-9-[[2-(heptyloxy)-1-(hydroxymethyl)ethoxy]methyl]-1,9-dihydro-6H-purin-6-one, mp >260°C, dec;

2,8-diamino-9-[[2-(hexyloxy)-1-(hydroxymethyl)ethoxy]methyl]-1,9-dihydro-6H-purin-6-one, mp 260-265°C, dec;
2,8-diamino-9-[[2-(cyclohexylmethoxy)-1-(hydroxymethyl)ethoxy]methyl]-1,9-dihydro-6H-purin-6-one, mp 242-247°C, dec;
2,8-diamino-1,9-dihydro-9-[[1-(hydroxymethyl)-2-(octyloxy)ethoxy]methyl]-6H-purin-6-one, mp >265°C, (dec);
2,8-diamino-1,9-dihydro-9-[[1-(hydroxymethyl)-2-(phenoxy)ethoxy]methyl]-6H-purin-6-one, mp 265-271°C, dec;
2,8-diamino-1,9-dihydro-9-[[2-hydroxy-1-[(4-methoxyphenoxy)methyl]ethoxy]methyl]-6H-purin-6-one;
2,8-diamino-1,9-dihydro-9-[[1-hydroxymethyl)-2-(4-methylphenoxy)ethoxy]methyl]-6H-purin-6-one; mp > 250°C, dec;
2,8-diamino-1,9-dihydro-9-[[2-(4-chlorophenoxy)-1-hydroxymethyl)ethoxy]methyl]-6H-purin-6-one, and
2,8-diamino-1,9-dihydro-9-[[[1-(hydroxymethyl)nonyl]oxy]methyl]-6H-purin-6-one.

EXAMPLE 5

9-[[2-Benzyloxy-1-(benzyloxymethyl)-ethoxy]methyl]-8-hydrazine-guanine

A mixture of 9-[[2-benzyloxy-1-(benzyloxymethyl)-ethoxy]methyl]guanine (2.1 g) [prepared according to K. K. Ogilvie, V. O. Cheriyan, B. K. Radatus, K. O. Smith, K. S. Galloway, and W. L. Kennell, Can J Chem, 60, 3005 (1982)] and N-bromosuccinimide (0.94 g) in acetic acid (21 ml) is stirred overnight and then is diluted with water and extracted with chloroform. The chloroform extract is dried and concentrated to give 2.3 g of yellow oil. The crude oil is suspended in ethanol (100 ml) and treated with 95% hydrazine. The solution is heated to reflux for 24 hours. The reaction mixture is then cooled and the product (0.75 g) filtered and dried, mp > 210° dec.

EXAMPLE 6

8-Amino-9-[[2-benzyloxy-1-(benzyloxymethyl)-ethoxy]-methyl]-guanine

A mixture of 9-[[2-benzyloxy-1-(benzyloxymethyl)-ethoxy)methyl]-8-hydrazine-guanine (0.45 g; 0.98 mmol), water (40 ml), ethanol (40 ml), ammonium hydroxide (20 ml) and Raney nickel (1 g) is heated to reflux for 24 hours. The catalyst is filtered off and the filtrate concentrated to a solid which is recrystallized from ethanol to give 0.16 g of analytical sample, mp 255-260° dec.

EXAMPLE 7

N-[9-[[1-(Butoxymethyl)-2-(phenylmethoxy)ethoxy]methyl]-6-hydroxy-9H-purin-2-yl]acetamide

Dry HCl (g) is bubbled into a stirred mixture of paraformaldehyde (1.45 g, 0.048 mol) and 1-butoxy-3-(phenylmethoxy)-2-propanol (5.0 g, 0.021 mol) in methylene chloride (57 ml) at 0°C until all the solid is dissolved. The resulting solution is stored at 0°C for 16 hours, dried over $MgSO_4$, and then evaporated to give chloromethyl glycerol ether as a very unstable clear oil. The clear oil is then added dropwise to a stirred mixture of potassium acetate (5.0 g, 0.051 mol) in acetone (60 ml). The mixture is stirred for 16 hours at room temperature and then filtered and evaporated. The residual oil is dissolved in toluene, washed with saturated $NaHCO_3$ and water, dried, and evaporated to give the acetoxy derivative as an oil (5.6 g) which is immediately used for condensation with diacetylguanine.

A mixture of diacetylguanine (4.6 g, 0.0195 mol) and crude acetoxy derivative from above (5.6 g), p-toluene sulfonic acid (43 mg) and sulfolane (5 ml)

is heated to 95°C under nitrogen atmosphere for 72 hours. At 24 hours and 48 hours, additional amounts of p-toluene sulfonic acid (20 mg each) are added. After 72 hours, the mixture is cooled, diluted with toluene and filtered. The filtrate is concentrated, chromatographed, and recrystallized from toluene to provide the desired product (1.33 g), mp 139-141°C.

EXAMPLE 8

The procedure described in Example 7 is repeated to prepare the following guanine-2-acetamide derivatives, starting from diacetylguanine and appropriate 1-(alkoxy or alkyl or substituted phenoxy)-3-(phenylmethoxy)-2-propanols in each case.

N-[6,9-dihydro-9-[[1-[(octyloxy)methyl]-2-(phenylmethoxy)ethoxy]methyl]-6-oxo-1H-purin-2-yl]-acetamide, mp 127-132°C;

N-[6,9-dihydro-6-oxo-9-[[1-(phenoxymethyl)-2-(phenylmethoxy)ethoxy]methyl]-1H-purin-2-yl]-acetamide, mp 144-146°C, and

N-[9-[[1-(ethoxymethyl)-2-(phenylmethoxy)ethoxy]methyl]-6,9-dihydro-6-oxo-1H-purin-2-yl]acetamide, mp 131-133°C, dec.

EXAMPLE 9

2-Amino-9-[[2-butoxy-1-(hydroxymethyl)ethoxy]methyl]-9H-purin-6-ol

A mixture of N-[9-[[1-(butoxymethyl)-2-(phenylmethoxy)ethoxy]methyl]-6-hydroxy-9H-purin-2-yl] acetamide (1.15 g, 25.9 mmol), 20% palladium on carbon (0.2 g), cyclohexene (20 ml), and ethanol (10 ml) is heated at reflux under N_2. After 8 and 20 hours, additional amounts of catalyst (0.1 g) are

added. After 36 hours, the solution is cooled, filtered through celite, and the filter cake is washed with DMF/ethanol. The filtrates are combined, refiltered and concentrated. The residue is mixed with aq. methyl amine (20 ml) and the mixture is heated at reflux for two hours, filtered and concentrated. The residue is recrystallized from water to give the desired product (0.7 g), mp 208-211°C.

EXAMPLE 10

The procedure described in Example 9 is repeated to prepare the following 9-substituted guanine derivatives, starting from N-[9-substituted-6-hydroxy-9H-purin-2-yl]acetamides in each case. Cyclohexene and cyclohexadiene can either be used in the transfer hydrogenation reaction:
2-amino-9-[[2-ethoxy-1-(hydroxymethyl)ethoxy]methyl]-1,9-dihydro-6H-purin-6-one, mp 206-209°C;
2-amino-1,9-dihydro-9[[1-(hydroxymethyl)-2-phenoxy-ethoxy]methyl]-6H-purin-6-one, mp 195-198°C, and
2-amino-1,9-dihydro-9-[[1-(hydroxymethyl)-2-(octyloxy) ethoxy]methyl]-6H-purin-6-one, mp 227-230°C.

EXAMPLE 11

2-Amino-9-[[1-[(heptyloxy)methyl]-2-[phenylmethoxy) ethoxy]methyl]-1,9-dihydro-6H-purin-6-one

A mixture of 2-amino-6-chloropurine (Aldrich Chemical Co.) 11.2 g, 0.066 mol) hexamethyldisilazane (160 ml), and ammonium sulfate (1.09 g) is refluxed for 2.5 hours and then cooled, concentrated and pumped to dryness. The residue is dissolved in dry toluene (210 ml) and is treated with $Hg(CN)_2$. The mixture is heated to 80°C and a solution of 2-(chloromethoxy)-1-(heptyloxy-3-(phenylmethoxy)

propane (prepared from 1-(heptyloxy)-3-(phenylmethoxy)-2-propanol (19 g, 0.068 mol), paraformaldehyde (4 g) and dry HCl (g) in CH_2Cl_2 (160 ml) as described in the first part of Example 7, in toluene (210 ml) is added to the solution and heated to 80-85°C for 2.5 hours. The mixture is cooled, concentrated, and diluted with CH_2Cl_2 (1.0 L) and is allowed to stand overnight. The CH_2Cl_2 solution is filtered, washed with 30% KI, 10% potassium carbonate solution and water. The organic layer is dried and concentrated. The residue is chromatographed over silica gel column using a high pressure liquid chromatographic instrument (Waters Prep 500). The column is eluted with ethyl acetate and hexane (1:1) to give the condensation product (i.e., chloropurine derivative) (6.45 g) which is hydrolysed as follows.

A mixture of the above chloropurine derivative (6.42 g, 0.0139 mol) methanol (150 ml) and sodium methoxide (3 g, 0.056 mol) is treated with mercaptoethanol (4.4 ml) and water (0.26 ml). The mixture is then heated to reflux under nitrogen for two hours and then an additional amount of sodium methoxide (1.9 g) is added. The reaction mixture is heated to reflux for an additional 4.0 hours, cooled, and concentrated to about 50 ml. The concentrate is diluted with water (120 ml) and the solution is acidified to pH 6.0. The solid precipitate is filtered, washed with water, and dried. The crude product is then recrystallized from methanol/water to give an analytical sample (4.25 g), mp 185-187°C.

EXAMPLE 12

The procedure described in Example 11 is repeated to prepare the following 9-substituted guanines starting from 2-amino-6-chloropurine and appropriate 1-(alkoxy or substituted phenoxy or

alkyl)-3-(phenylmethoxy)-2-propanols in each case:
2-amino-9-[1-[(cylcohexylmethoxy)methyl]-2-(phenylmethoxy)ethoxy]methyl]-1,9-dihydro-6H-purin-6-one, mp 198-201°C;
2-amino-9-[1-[(hexyloxy)methyl]-2-(phenylmethoxy)ethoxy]methyl]-1,9-dihydro-6H-purin-6-one; mp 192-194°C.
2-amino-1,9-dihydro-9-[1-[(pentyloxy)methyl]-2-(phenylmethoxy)ethoxy]methyl]-6H-purin-6-one, mp 192-194°C;
2-amino-1,9-dihydro-9-[-1-[(octyloxy)methyl]-2-(phenylmethoxy)ethoxy]methyl]-6H-purin-6-one, mp 184-186°C;
2-amino-1,9-dihydro-9-[1-(phenoxy)methyl)-2-(phenylmethoxy)ethoxy]methyl]-6H-purin-6-one;
2-amino-1,9-dihydro-9-[[[1-[(phenylmethoxy)methyl]hexyl]oxy]methyl-6H-purin-6-one, mp 206-208°C;
2-amino-1,9-dihydro-9[[[1-[(phenylmethoxy)methyl]nonyl]oxy]methyl-6H-purin-6-one, mp 205-207°C;
2-amino-9-[1-[(4-chlorophenoxy)methyl]-2-[phenylmethoxy]ethoxy]methyl]-1,9-dihydro-6H-purin-6one, mp >210°C;
2-amino-1,9-dihydro-9-[1-[(4-methoxyphenoxy)methyl]-2-[phenylmethoxy]ethoxy]methyl]-6H-purin-6-one, mp 150-156°C, and
2-amino-1,9-dihydro-9-[1-[(4-methylphenoxy)methyl]-2-[phenylmethoxy]ethoxy]methyl]-6H-purin-6-one, mp 198-200°C.

EXAMPLE 13

2-Amino-9-[[2-(heptyloxy)-1-(hydroxymethyl)ethoxy]methyl]-1,9-dihydro-6H-purin-6-one

A mixture of 2-amino-9-[1-[(heptyloxy)methyl]-2-(phenylmethoxy)ethoxy]methyl]-1,9-dihydro-6H-purin-6-one (3.9 g, 8.97 mmol), ethanol (200 ml), cyclohexadiene (87 ml, 92.3 mmcl), and 20% palladium

on charcoal (1.5 g) is heated to reflux under nitrogen atmosphere. After seven hours an additional amount of 20% palladium on charcoal (0.5 g) is added and the mixture is heated to reflux for a total of 18 hours. The mixture is filtered hot and then allowed to cool. The solid formed is collected and dried to give the desired purine (1.95 g), mp 224-225°C.

EXAMPLE 14

The procedure described in Example 13 is repeated to prepare the following 9-substituted guanines starting from appropriate phenylmethoxy derivatives described in Example 11 and 12.

2-amino-1,9-dihydro-9-[[[1-(hydroxymethyl)hexyl]oxy]methyl]-6H-purin-6-one, mp 228-229°C;

2-amino-1,9-dihydro-9-[[[1-(hydroxymethyl)nonyl]oxy]methyl]-6H-purin-6-one, mp >250°C, dec;

2-amino-9-[[2-(ethoxy)-1-(hydroxymethyl)ethoxy]methyl]-1,9-dihydro-6H-purin-6-one, mp 206-209°C;

2-amino-9-[[2-(butoxy)-1-(hydroxymethyl)ethoxy]methyl]-9H-purin-6-ol, mp 208-211°C;

2-amino-9-[[2-(hexyloxy)-1-(hydroxymethyl)ethoxy]methyl]-1,9-dihydro-6H-purin-6-one;

2-amino-1,9-dihydro-9-[[1-(hydroxymethyl)-2-(penyloxy)ethoxy]methyl]-6H-purin-6-one, mp 218-220°C;

2-amino-1,9-dihydro-9-[[1-(hydroxymethyl)-2-(octyloxy)ethoxy]methyl]-6H-purin-6-one, mp 227-230°C;

2-amino-9-[[2-(cyclohexylmethoxy)-1-(hydroxymethyl)ethoxy]methyl]-1,9-dihydro-6H-purine-6-one, mp > 260°C, dec;

2-amino-1,9-dihydro-9-[[1-(hydroxymethyl)-2-phenoxyethoxy]methyl]-6H-purin-6-one, mp 195-198°C;

2-amino-1,9-dihydro-9-[[1-(hydroxymethyl)-2-(4-methylphenoxy)ethoxy]methyl]-6H-purin-6one, mp 206-208°C;

2-amino-1,9-dihydro-9-[[2-(hydroxy-1-[(4-methoxy-phenoxy)methyl]ethoxy]methyl]-6H-purin-6-one, mp 210-217°C, dec, and

2-amino-9-[[2-(4-chlorophenoxy)-1-(hydroxymethyl) ethoxy]methyl]-1,9-dihydro-6H-purin-6-one,

SYNTHESIS OF STARTING MATERIALS

EXAMPLE A

1-Butoxy-3-(phenylmethoxy)-2-propanol

n-Butanol (2.5 ml, 27 mmol) is added to a suspension of sodium hydride (50% in mineral oil; 1.3 g, 27 mmol) in DMF (5 ml) and the mixture is then heated to 80°C for 1.0 hours when all the sodium hydride is consumed. A solution of 2,3-epoxypropyl benzyl ether (benzyl glycidylether*) (4.52 g, 27 mmol) in DMF (5 ml) is added slowly to the n-butoxide solution. The mixture is then heated to 80°C for 16 hours, diluted with water and extracted with ether. The ether layer is dried and concentrated to give an oil which is distilled to provide the desired product (3.1 g), bp 125-130°/0.8-0.5 mm.

EXAMPLE B

The procedure described in Example A is repeated to prepare the following 1-alkoxy or aryloxy-3-(phenylmethoxy)-2-propanols, starting from appropriate alkanols or phenols in each case.

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*Benzyl glycidyl ether is prepared according to the published procedure (J. R Bacon and M. J. Collis, Chem. and Ind., 1971, 930) or purchased from commercial source.

1-(ethoxy)-3-(phenylmethoxy)-2-propanol, bp 92-99°C/ 0.25-0.3 mm;
1-(pentyloxy)-3-(phenylmethoxy)-2-propanol, bp 115-118°C/0.3 mm;
1-(hexyloxy)-3-(phenylmethoxy)-2-propanol, bp 123-125°C/0.12 mm;
1-(heptyloxy)-3-(phenylmethoxy)-2-propanol, bp 141°C/0.36 mm, and
1-(octyloxy)-3-(phenylmethoxy)-2-propanol, bp 150-155°C/0.7 mm.

EXAMPLE C

1-(Phenylmethoxy)-2-decanol

Benzyl alcohol (108 g, 1.0 mol) is added to a suspension of 50% sodium hydride-mineral oil (48 g, 1.0 mol) in DMF (200 ml) at room temperature. The mixture is then heated to 80°C for two hours. A solution of 1,2-epoxydecane* (85 ml) in DMF (50 ml) is added slowly to the sodium salt over 30 minutes and the mixture is then heated at 80°C for 20 hours. The reaction mixture is cooled, diluted with water, neutralized with acetic acid, and extracted with ether. The ether extract is concentrated to give an oil which is distilled to give the desired product (131 g), bp 178-180°C/4 mm.

EXAMPLE D

The procedure described in Example C is repeated to prepare the following 1-(phenylmethoxy)-alkanols, starting from appropriate 1,2-epoxides in each case.

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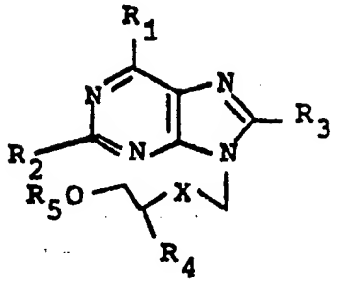
*Purchased from Aldrich Chemical Co. Other epoxides are either purchased or prepared from olefin or epichlorohydrine as the case may be.

1-(cyclohexylmethoxy)-3-(phenylmethoxy)-2-propanol, bp 136-139°C/0.24-0.22 mm;
1-(phenylmethoxy)-2-heptanol, bp 125-130°C/3-5 mm;
1-(phenoxy)-3-(phenylmethoxy)-2-propanol, bp 148-157°C/0.32 mm;
1-(4-methylphenoxy)-3-(phenylmethoxy)-2-propanol, bp 194°C/2 mm;
1-(4-methoxyphenoxy)-3-(phenylmethoxy)-2-propanol, bp 175-184°C/0.4 mm, and
1-(4-chlorophenoxy)-3-(phenylmethoxy)-2-propanol, bp 188-190°C/1.2-1.3 mm.

CLAIMS (f r: BE, CH, DE, FR, GB, IT, LI, LU, NL, SE)

1. A comp und having the following general formula:



or a tautomeric isomer thereof or a pharmaceutically acceptable base salt or acid addition salt thereof, wherein:

R_1 is -OH or -SH;

R_2 is a hydrogen atom or -NHR in which R is hydrogen or $-COR_6$;

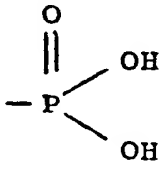
R_6 is a C_{1-4} alkyl radical, an aryl radical or an aralkyl radical;

R_3 is a bromine or NHR where R is hydrogen or COR_6;

X is an oxygen or a sulphur atom;

R_4 is a hydrogen atom or $-CH_2OR_5$; and

R_5 is hydrogen, a C_{1-8} alkyl radical, an aralkyl radical, an aryl radical, $-COR_6$ or



;

with the proviso that when R_1 is -OH, R_2 is $-NH_2$, R_3 is a bromine atom and R_5 is a hydrogen atom, R_4 is not a hydrogen atom.

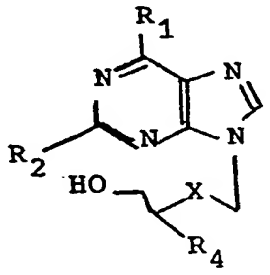
2. A compound according to Claim 1, or a tautomeric isomer thereof or a pharmaceutically acceptable base or acid addition salt thereof, wherein: R_6 is a C_{1-4} alkyl radical or a phenyl radical; R_3 is bromine or NH_2; and R_5 is a

hydrogen atom, a C_{1-8} radical, a phenyl radical, or a benzyl radical.

3. A compound according to Claim 1 or 2, wherein: R_1 is -OH; R_2 is hydrogen or $-NH_2$; R_3 is bromine or $-NH_2$; X is an oxygen atom; R_4 is a hydrogen atom or $-CH_2OR_5$; and R_5 is a hydrogen atom.

4. A compound according to Claim 1, and being
2,8-diamino-9-[(2-hydroxyethoxy)methyl]-9H-purin-6-ol;
2-[(2,8-diamino-6-hydroxy-9H-purin-9-yl)methoxy]-1,3-propanediol;
2-[(2-amino-8-bromo-6-hydroxy-9H-purin-9-yl)-methoxy]-1,3-propanediol;
2,8-diamino-1,9-dihydro-9-[[1-(hydroxymethyl)-2-phenoxyethoxy]methyl]-6H-purin-6-one.

5. A compound having the following general formula:



or a tautomeric isomer thereof, or a pharmaceutically acceptable acid or base addition salt thereof, wherein:

R_1 is -OH or -SH;

R_2 is a hydrogen atom or -NHR in which R is hydrogen or $-COR_6$;

R_6 is a C_{1-4} alkyl radical, an aryl radical or an aralkyl radical;

X is an oxygen or sulphur atom; and

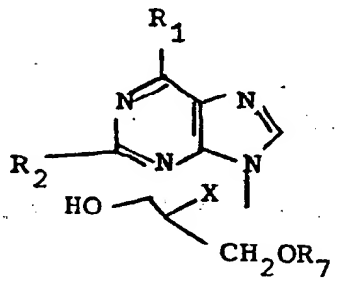
R_4 is a C_{1-8} alkyl radical, an aryl radical or an aralkyl radical.

6. A compound according to Claim 5, wherein: R_1 is -OH; R_6 is a C_{1-4} alkyl radical, a phenyl

or benzyl radical; X is an oxygen atom; and R_4 is a C_{1-8} alkyl radical, a phenyl or benzyl radical.

7. A compound according to Claim 6, wherein: R_6 is a methyl radical; and R_4 is a C_{1-8} alkyl radical, a phenyl or benzyl radical.

8. A compound having the following general formula:



or a tautomeric isomer thereof, or a pharmaceutically acceptable acid or base salt thereof, wherein:

R_1 is -OH or -SH;

R_2 is a hydrogen atom or -NHR in which R is a hydrogen atom or $-COR_6$;

R_6 is a C_{1-4} alkyl radical, an aryl radical or an aralkyl radical;

X is an oxygen or sulphur atom; and

R_7 is a C_{1-8} alkyl radical, a cycloalkyl radical of from five to seven ring members, a cylcoalkylalkyl radical, an aryl radical, or an aralkyl radical.

9. A compound according to Claim 8, wherein: R_1 is -OH; R_6 is a C_{1-4} alkyl radical, a phenyl or a benzyl radical; X is an oxygen atom; and R_7 is a C_{1-8} alkyl radical, a cycloalkyl radical of five to seven ring members, a cycloalkylalkyl radical, a phenyl or a benzyl radical.

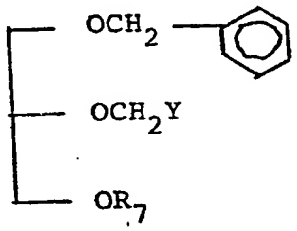
10. A compound according to Claim 9, wherein: R_6 is a methyl radical; and R_7 is a C_{1-8} alkyl radical, a cyclopentyl, a cyclohexyl, a

cyclopentylmethyl, a cyclohexylmethyl, a phenyl or a benzyl radical.

11. A compound according to Claim 10, and being 2-amino-9-[[2-(heptyloxy)-1-(hydroxymethyl)ethoxy] methyl]-1,9-dihydro-6H-purin-6-one; 2-amino-1,9-dihydro-9-[[1-(hydroxymethyl)-2-phenoxyethoxy]methyl]-6H-purin-6-one.

12. A pharmaceutical composition comprising a compound according to any preceding claim, in admixture with a pharmaceutically acceptable carrier or diluent.

13. A compound having the following general formula:

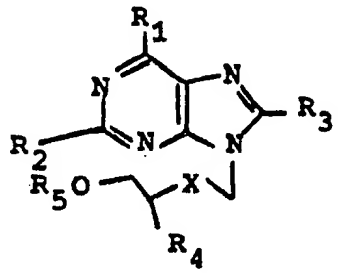


wherein: Y is an acetyloxy or a chloro radical; and R_7 is a C_{1-8} alkyl radical, a cycloalkyl radical of from five to seven ring members, a cycloalkylalkyl, an aryl or an aralkyl radical.

14. A compound according to Claim 13, wherein: R_7 is a C_{1-8} alkyl radical, a cyclopentyl, a cyclohexyl, a cyclopentylmethyl, a cyclohexylmethyl or a phenyl radical.

CLAIMS (for: AT)

1. A process for preparing a compound having the following general formula:



or a tautomeric isomer thereof or a pharmaceutically acceptable base salt or acid addition salt thereof, wherein:

R_1 is -OH or -SH;

R_2 is a hydrogen atom or -NHR in which R is hydrogen or $-COR_6$;

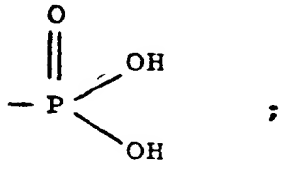
R_6 is a C_{1-4} alkyl radical, an aryl radical or an aralkyl radical;

R_3 is a bromine or NHR where R is hydrogen or COR_6;

X is an oxygen or a sulphur atom;

R_4 is a hydrogen atom or $-CH_2OR_5$; and

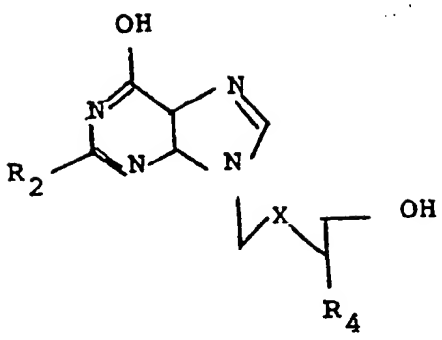
R_5 is hydrogen, a C_{1-8} alkyl radical, an aralkyl radical, an aryl radical, $-COR_6$ or



;

with the proviso that when R_1 is -OH, R_2 is $-NH_2$, R_3 is a bromine atom and R_5 is a hydrogen atom, R_4 is not a hydrogen atom;

which process comprises brominating a compound of the formula



to give the 8-substituted bromo compound; optionally treating the 8-bromo compound with hydrazine and reducing the 8-hydrazine compound to the 8-amino compound; optionally converting the 8-amino compound to the 8-$NHCOR_6$ compound; optionally converting the 8-bromo, 8-amino or 8-$NHCOR_6$ compound to the compound wherein R_1 is -SH, and/or R_5 is as defined above: and optionally forming the pharmaceutically acceptable base or acid addition salt.

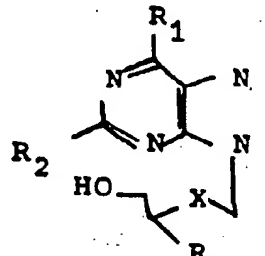
2. A process according to Claim 1, wherein: R_6 is a C_{1-4} alkyl radical or a phenyl radical; R_3 is bromine or NH_2; and R_5 is a hydrogen atom, a C_{1-8} radical, a phenyl radical, or a benzyl radical.

3. A process according to Claim 1 or 2, wherein: R_1 is -OH; R_2 is hydrogen or $-NH_2$; R_3 is bromine or $-NH_2$; X is an oxygen atom; R_4 is a hydrogen atom or $-CH_2OR_5$; and R_5 is a hydrogen atom.

4. A process according to Claim 1, for preparing a compound having the name
2,8-diamino-9-[(2-hydroxyethoxy)methyl]-9H-purin-6-ol;
2-[(2,8-diamino-6-hydroxy-9H-purin-9-yl)methoxy]-1,3-propanediol;
2-[(2-amino-8-bromo-6-hydroxy-9H-purin-9-yl)-methoxy]-1,3-propanediol;

2,8-diamino-1,9-dihydro-9-[[1-(hydroxym thyl)-2-phenoxyethoxy]methyl]-6H-purin-6-one.

5. A process for preparing a compound having the following general formula:



or a tautomeric isomer thereof, or a pharmaceutically acceptable acid or base addition salt thereof, wherein:

R_1 is -OH or -SH;

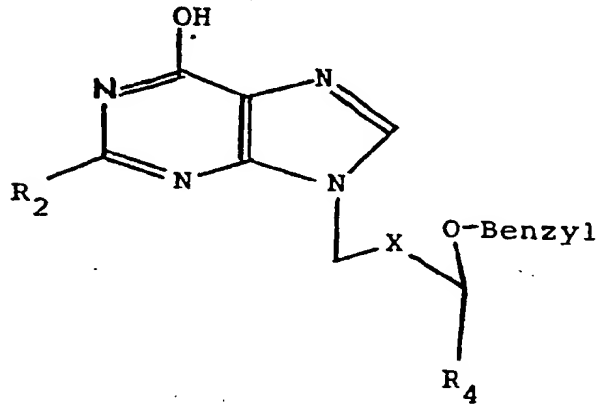
R_2 is a hydrogen atom or -NHR in which R is hydrogen or $-COR_6$;

R_6 is a C_{1-4} alkyl radical, an aryl radical or an aralkyl radical;

X is an oxygen or sulphur atom; and

R_4 is a C_{1-8} alkyl radical, an aryl radical or an aralkyl radical;

which process comprises reducing the benzyloxy group of a compound of the following formula to a hydroxy group:



optionally forming, by known methods, the compound wherein R_1 is SH; and optionally forming the pharmaceutically acceptable base and acid addition

salts thereof.

6. A process according to Claim 5, wherein: R_1 is -OH; R_6 is a C_{1-4} alkyl radical, a phenyl or benzyl radical; X is an oxygen atom; and R_4 is a C_{1-8} alkyl radical, a phenyl or benzyl radical.

7. A process according to Claim 6, wherein: R_6 is a methyl radical; and R_4 is a C_{1-8} alkyl radical, a phenyl or benzyl radical.

8. A process according to Claim 5, wherein R_4 is additionally chosen from a $-CH_2OR_7$ radical wherein: R_7 is a C_{1-8} alkyl radical, a cycloalkyl radical of from five to seven ring members, a cylcoalkylalkyl radical, an aryl radical, or an aralkyl radical.

9. A process according to Claim 8, wherein: R_1 is -OH; R_6 is a C_{1-4} alkyl radical, a phenyl or a benzyl radical; X is an oxygen atom; and R_7 is a C_{1-8} alkyl radical, a cycloalkyl radical of five to seven ring members, a cycloalkylalkyl radical, a phenyl or a benzyl radical.

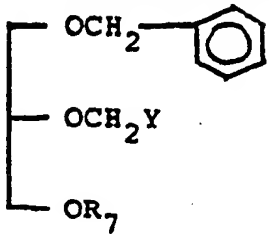
10. A process according to Claim 9, wherein: R_6 is a methyl radical; and R_7 is a C_{1-8} alkyl radical, a cyclopentyl, a cyclohexyl, a cyclopentylmethyl, a cyclohexylmethyl, a phenyl or a benzyl radical.

11. A process according to Claim 10, for preparing a compound having the name 2-amino-9-[[2-(heptyloxy)-1-(hydroxymethyl)ethoxy]methyl]-1,9-dihydro-6H-purin-6-one; 2-amino-1,9-dihydro-9-[[1-(hydroxymethyl)-2-phenoxyethoxy]methyl]-6H-purin-6-one;

12. A process for preparing a pharmaceutical composition, which process comprises combining a compound prepared by a process as claimed in any preceding claim with a pharmaceutically acceptable carrier or diluent.

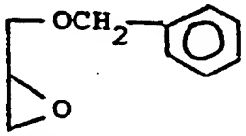
13. A process for preparing a compound

having the following general formula:

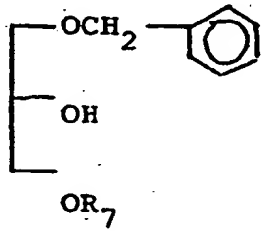


wherein: Y is an acetyloxy or a chloro radical; R_7 is a C_{1-8} alkyl radical, a cycloalkyl radical of from five to seven ring members, a cycloalkylalkyl, an aryl or an aralkyl radical;

which process comprises treating a compound having the formula



with an oxide of the formula R_7O^- to give a compound having the formula



subsequently converting the hydroxyl group to a $-OCH_2Cl$ group and optionally converting the thus formed $-OCH_2Cl$ group to an acetyloxy radical.

14. A process according to Claim 13, wherein: R_7 is a C_{1-8} alkyl radical, a cyclopentyl, a cyclohexyl, a cyclopentylmethyl, a cyclohexylmethyl or a phenyl radical.

European Patent Office

EUROPEAN SEARCH REPORT

0145207

Application number

EP 84307373.5

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
X	CH - A5 - 623 587 (THE WELLCOME FOUNDATION LIMITED) * Page 2, right column, line 43 - page 3, right column, line 44 * --	5-10,12	C 07 D 473/18 C 07 C 43/174 C 07 C 43/192 C 07 C 69/12 A 61 K 31/52
X	EP - A1 - 0 049 072 (ENS BIOLOGICALS INC.) * Claims 1,6,13,15 * --	8-10,12	
P,X	DE - A1 - 3 234 610 (SCHERING AG) * Claims 1,2 * --	13	
D,A	JOURNAL OF MEDICINAL CHEMISTRY, vol. 26, no. 5, May 1983 J.C. MARTIN et al. "9-[(1,3-Dihydroxy-2-propoxy) methyl]guanine: A New Patent and Selective Anti-herpes Agent" pages 759-761 * Pages 759, 760 * --	8-10,12 13	TECHNICAL FIELDS SEARCHED (Int. Cl.4) C 07 D 473/00 C 07 C 43/00 C 07 C 69/00
D,A	BIOCHEMICAL PHARMACOLOGY, vol. 30, no. 13, July 1, 1981 P.M. KELLER et al. "Enzymatic phosphorylation of acyclic nucleoside analogs and correlations with antiherpetic activities" pages 3071-3077 * Page 3073, compound no. 22 * --	1,3,12	

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
VIENNA	04-01-1985	HERING

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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DOCUMENTS CONSIDERED TO BE RELEVANT

EP 84307373.5

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D,A	CANADIAN JOURNAL OF CHEMISTRY, vol. 60, no. 24, December 15, 1982 K.K. OGILVIE et al. "Biologically active acyclonucleoside analogues. II. The synthesis of 9-[[2-hydroxy-1-(hydroxymethyl)-ethoxy]methyl] guanine (BIOLF-62)" pages 3005-3010 * Pages 3006, 3007 * --	8-10, 12,13	
A	GB - A - 1 567 671 (THE WELLCOME FOUNDATION LIMITED) * Page 1, lines 15-33; claim 1 * ----	1-3,12	
			TECHNICAL FIELDS SEARCHED (Int. Cl.4)

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